Journal of Clinical Monitoring and Computing (2006) 20: 251–260
DOI: 10.1007/s10877-006-9029-9

MONITORING OF FUNCTIONAL RESIDUAL CAPACITY BY AN OXYGEN WASHIN/WASHOUT; TECHNICAL DESCRIPTION AND EVALUATION

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Weismann D, Reißmann H, Maisch S, Füllekrug B, Schulte am Esch J. Monitoring of functional residual capacity by an oxygen washin/washout; technical description and evaluation.
J Clin Monit Comput 2006; 20: 251–260

ABSTRACT. Objective. It was the goal of this study to develop and test an automated method for measuring functional residual capacity (FRC) by an oxygen washin/washout in intensive care settings. Such a method is required to work with conventional ventilator breathing systems and to use only medical grade sensors. **Methods.** The oxygen setting on a standard intensive care ventilator is changed by at least 10%. Ventilatory pressure and flow are measured by the built-in sensors of the intensive care ventilator. Oxygen concentration is measured by a diverting medical oxygen analyzer. In order to overcome the known problem that synchrony between flow and concentration measurement is corrupted by the change of gas viscosity and by the cyclic change of airway pressure, a physical/mathematical model of the pneumatic circuit of the analyzer was developed. With this model, the change of sample flow is calculated continuously. Thus, synchrony between flow and gas concentration measurement is restored. This allows the determination of volumetric gas fluxes as needed for the FRC measurement. The setup was tested in the laboratory with a lung simulator. Simulated lung compliance, breathing frequency and tidal volume were varied. **Results.** The mean difference between measured and simulated FRC (range 1.7 to 5 L) was less than 1% at tidal volumes greater than 400 mL. This difference ranged from −5% to 8%, depending on simulated lung compliance and ventilator setting. The variability of consecutive measurements was about 2.5%. **Conclusions.** A method has been developed for reliable measurement of the FRC with an oxygen washin/washout technique. This method is sufficiently easy to use to suit for application in intensive care units. It does not require any action by the operator except a manual change of inspired oxygen concentration. Accuracy and sensitivity of the method have been proven sufficient to meet clinical and scientific requirements. Future clinical studies will reveal the applicability of the chosen procedure under clinical conditions.

KEY WORDS. functional residual capacity, oxygen washin/washout, mechanical ventilation.

INTRODUCTION

The FRC of the lungs is reduced in many forms of acute respiratory failure as well as in general anesthesia. Restoration of a normal FRC by appropriate settings for PEEP and by maneuvers to re-open a collapsed lung is one of the dominant principles of respiratory therapy. Therefore, knowledge of the FRC could be valuable for optimizing mechanical ventilation in the intensive care setting.

The lack of a simple and preferably automated technique has so far limited the acceptance of measuring FRC in the intensive care patient [1]. Although various methods have been published during the last decades [2–10], none

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Received 28 August 2005 and Accepted for publication 14 April 2006.

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of them proved to be sufficiently affordable, simple, and robust for routine bedside use. Therefore, FRC is presently determined mainly in scientific studies.

Inert Gas Dilution in a closed system is commonly used in lung function labs with spontaneously breathing patients. However, this technique cannot be adapted to intensive care ventilators without major modifications to the breathing system. The washin/washout of inert tracer gases, like e.g. SF_6, in an open system allows precise measurements, but requires a dispensing device that delivers the tracer gas in proportion to the instantaneous inspiratory flow so that the inspiratory concentration is held constant regardless of the inspiratory flow pattern. The need for an additional gas tank may further impede the acceptance of this technique for routine use. Frequently, nitrogen is used as indicator gas. It is inert and has a nearly negligible solubility in blood. However, affordable nitrogen sensors that can be used in a clinical environment are not available. In contrast, fast medical sensors for the complementary gas oxygen are available at moderate cost and are already part of some respiratory gas monitors. Nitrogen has the advantage over oxygen of not being metabolized, thus methods based on it are not directly affected by changes in metabolism during the procedure. However, both are affected by errors arising from the shift of oxygen between alveolar gas and blood caused by changes of FiO_2 (Appendix A).

Despite these limitations, we devised and tested an FRC monitor based on oxygen washin and washout. This work is based on the previous work by Mitchell *et al.* [2]. State of the art technology and microprocessor based computation power enabled us to solve problems that could not be tackled previously or were not apparent at Mitchell's time. The greatest problem to be solved results from the lack of a suitable mainstream sensor for synchronous measurement of flow and gas concentration. Instead, a side-stream sensor had to be used. Such sensors impose a significant delay between flow and gas concentration measurement. Unfortunately, this delay is not constant. It is affected by the viscosity of the sampled gas [8]. which depends on the oxygen concentration. In addition, it alternates during each breath of positive pressure ventilation [11] because of the fluctuating pressure gradient across the sampling tube. This required sophisticated corrections for the variable measurement delay as outlined in Appendix B.

MATERIALS AND METHODS

Experimental set-up

The ventilator (EVITA-4, Dräger Medical, Lübeck, Germany) was connected to a test lung using standard respiratory tubing. Pressure and flow were measured by the sensors integral to the ventilator whereas oxygen concentration was measured with a fast paramagnetic sensor (Pm1111E, Servomex Group Ltd.) in the side-stream. The response time T_{10-90} of this sensor to a step change of O_2-concentration is about 200 ms. Sample flow was adjusted to 200 mL/min, which is close to the maximum flow recommended by the manufacturer of this transducer. This led to a pressure drop across the sampling tube of about 50 mbar. Data were acquired at a rate of 125 Hz and analyzed on-line. For the measurement of FRC, the inspired oxygen concentration (F_iO_2) was altered from 21% to 60%, from 60% to 100% and back. Each sequence was repeated 3 times yielding 12 measurements, 6 during washin and 6 during washout. This great change of the F_iO_2 was chosen in order to generate a great change of the viscosity of the sample gas, thereby introducing a significant change of the sample delay of about 50 ms.

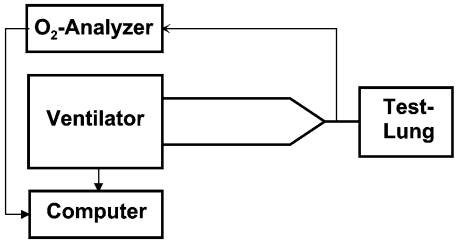

Fig. 1. Schematic diagram of the setup.

The computer program determines continuously all data needed for the FRC determination, i.e. inspired and expired volumes, mean inspiratory and expiratory oxygen concentrations and the end-expiratory concentration. The calculation of the FRC starts automatically after a small change of inspired oxygen concentration that is followed by a steady state change of at least 10% F_iO_2 (20% recommended). The program calculates and displays a new value of the FRC after each breath from the data acquired so far. The calculation is terminated when the accumulated net ventilated volume (sum of tidal volume minus serial dead-space) is greater than eight times the calculated FRC.

For the majority of the measurements an electromechanical test lung (LS 4000, Dräger Medical, Lübeck, Germany) was used. This test lung can be used for simulated spontaneous breathing as well as for controlled ventilation. It consists of a motor driven bellows. Compliance, resistance and volume of this test lung can be adjusted electronically. The end-expiratory volume could be varied from about 1.7 L to 5 L. Gas mixing in this test lung was enforced by a fan. A serial dead space of 160 mL was simulated by two breathing filters arranged in series, connected to a 7.5 mm endotracheal tube. Since the minimum volume of this test

lung could not be determined accurately, absolute accuracy of the measurements was determined in a separate experiment. An anesthesia bag was placed in a water bath. The volume of this bag was determined from the change of water level. Different levels of PEEP were used to change its volume.

Procedure and choice of parameters

Patients whose FRC is measured will have various mechanical properties of their respiratory system. They will also be ventilated with various ventilation modes. Therefore, tests of equipment should be performed under all possible combinations of lung mechanics and ventilator setting. However, this is neither feasible nor needed. Instead, it is preferable to investigate the limitations of the chosen procedure under worst-case conditions; these are conditions where the disturbing effects requiring correction are expected to have the biggest impact. As outlined in the appendix, the greatest adverse effect is caused by the cyclic change of airway pressure, which corrupts the synchrony between the measured flow and gas concentration. Therefore, worst-case situations are those where the pressure swing is high, the pressure changes quickly and the time-constant of the lung is short. The chosen combinations of simulated lung compliance and ventilator setting and the results are summarized in Table 1.

In a first series of measurements, the sensitivity to detect changes of the FRC was verified under favorable conditions. The lung simulator was simulating spontaneous breathing. Since the pressure at the Y-piece was constant, the only effect that could alter the delay slightly was the changing viscosity of the gas, which caused a delay change by about 50 ms. The breathing pattern was sinusoidal, which further reduced the influence of any delay change. These measurements under favorable conditions served mainly as a reference for the subsequent measurements under more challenging patterns of ventilation.

Absolute accuracy was verified in a second series using an anesthesia bag placed in a water bath. FRC was varied between 0.4 and 2 L. These measurements were performed under controlled ventilation with a tidal volume of 600 mL and a frequency of 10 bpm.

After these initial reference-measurements, accuracy and repeatability were tested under challenging conditions. Compliance of the simulator, tidal volume and frequency were varied within a wide range. If not stated otherwise all measurements were performed over the whole range of the adjustable FRC, i.e. from 1.7 L to 5 L.

RESULTS

The correlation coefficient between measured FRC and simulated FRC was always greater than $r = 0.999$ for those measurements where the simulated FRC was varied. In all experiments except one, all errors were proportional to the simulated FRC. Therefore, the data are presented in Table 1 as relative errors: (a) difference between measured and simulated FRC; (b) variability (1 SD); (c) asymmetry, i.e. the difference of the calculated FRC between washin and washout. Separate determination of the variability for washin or washout, respectively, yielded a value of about 2/3 of the stated variability.

Reference measurements

Series 1: Figure 2 shows the measured FRC versus the volume signal from the test lung. The mean difference between measured and simulated FRC change was less than 2%, which is within the accuracy limits of the calibration of the test lung and the ventilator. Variability was 2%, asymmetry 2.4%.

Series 2: Here the volume of the anesthesia bag served as reference. The regression between measured FRC and

Table 1. Summary of measurement conditions and results

Ventilation mode	Spont.	CMV	CMV	CMV	CMV	CMV	PCV	PCV	CMV
Compliance [mL/mbar]	100	bag	50	20	50	50	50	20	35
Frequency [b.p.m]	12	10	15	15	30	25	25	25	10.30
Peak pressure [mbar]	0	<10	23	50	16	44	30	30	var.
Plateau pressure [mbar]	0	<10	16	42	10	22	30	30	var.
Peak insp.-flow [L/min]	40	18	35	35	35	80	80	60	var.
Peak exp. flow [L/min]	35	20	55	100	30	75	60	60	var.
Tidal volume [mL]	1000	600	800	800	400	1000	800	400	440–1000
Mean FRC error [%]			+1.0	−5.3	+2.5	−1.7	−0.5	+7.2	1.8
Variability [%]	2.0	3.3	2.6	2.6	1.6	1.8	2.4	3.3	2.3
Asymmetry [%]	2.4	−2.3	3.5	3.7	0.5	0.4	3.2	−5.1	−1.9

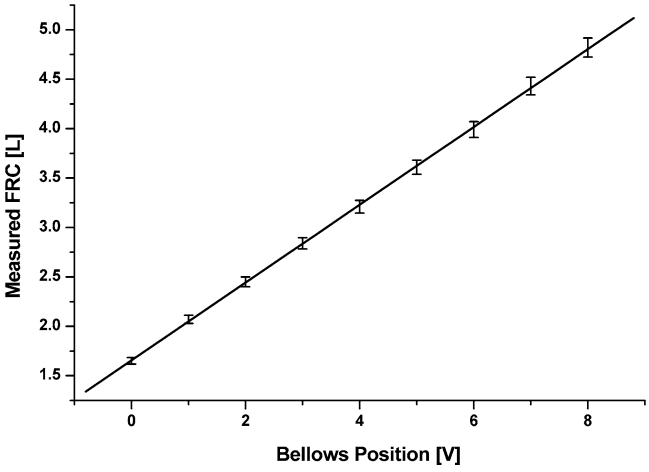

Fig. 2. Measured FRC as function of the end-expiratory bellows position. A voltage change of 1 V is equivalent to a change of the simulated FRC by 400 mL.

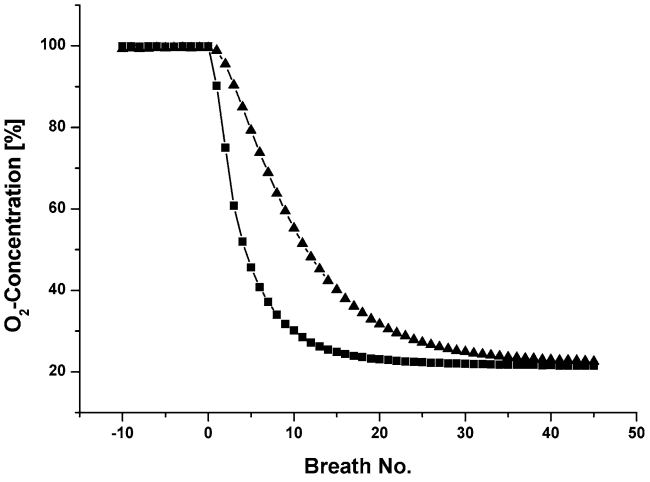

Fig. 3. End-inspiratory (squares) and end-expiratory (triangles) O_2-concentration measured with an empty large volume humidifier in the inspiratory limb of the tubing system during washout.

reference is given by $\mathrm{FRC}_{\mathrm{meas}} = -35\,\mathrm{mL} + 0.95 \times \mathrm{FRC}_{\mathrm{ref}}$. Variability was 3.3%, asymmetry −2.3%.

Variation of lung mechanics and breathing pattern

Series 3: The conditions chosen in this series are typical for the ventilation of patients with normal or moderately restricted lungs. There was no significant difference between measurement and reference.

Series 4: The conditions of these measurements are clinically unrealistic worst-case conditions. Compliance was drastically reduced. Although such severely restricted lungs are usually ventilated with smaller volumes and lower pressures, tidal volume and frequency were kept normal. Typical for these measurements was (1) a low inspiratory flow leading to a relatively slow pressure increase during inspiration and (2) an immediate pressure drop at the onset of expiration associated with a high peak expiratory flow. Under these unfavorable conditions, the FRC was systematically underestimated by about 5%. However, reproducibility and asymmetry were essentially unchanged, compared with the reference measurements. These measurements were repeated with an empty Aquapor humidifier (Dräger Medical) inserted into the inspiratory limb of the tubing system. The high volume of this humidifier retarded the washin of oxygen into the tubing system significantly as shown in Figure 3. However, both measurements gave the same results.

Series 5: With this combination, we investigated whether a reduction of tidal volume with concurrent increase of frequency affects the measurement. We observed a minor overestimation of the FRC by 2.5%.

Series 6: During previous measurements the speed of pressure increase during inspiration was always much slower than that of the decrease at the onset of expiration. The difference between peak and plateau pressure was small. In this series, we investigated whether a changed pressure pattern with a high peak to plateau difference has an influence on the results. The mean error of −1.7% was negligible; reproducibility and asymmetry were essentially unchanged.

Series 7: In this series, compliance and tidal volume were identical to those of series 3. However, because of the high frequency inspiratory flow and ventilatory pressure were increased. At the end of inspiration, the inspiratory flow amounted to 50% of the peak flow. All error parameters were essentially unchanged compared with that of the reference measurements.

Series 8: Here the compliance was set to an extremely low value of 20 mL/mbar, leading to a very short time constant of the lung. Inspiratory and expiratory peak flows were very high. Therefore, the accuracy of the corrections is expected to have a great influence. Measurement was performed up to an FRC of 3.5 L. In contrast to all other measurements, the relative error increased with increasing FRC. It increased from 4% (70 mL) at 1.7 L to 10% (350 mL) at 3.5 L FRC. Reproducibility was slightly reduced. The asymmetry of −5.1% revealed the technical limitations of the investigated system under these extreme conditions.

Series 9: These measurements were performed with a compliance of about 35 mL/mbar. Alveolar ventilation was kept constant at 8.4 l/min (serial dead space 160 mL). Tidal volume was 1000 mL at 10 bpm and 440 mL at 30 bpm.

FRC was kept constant at 1.65 l. It was the aim of these measurements to investigate selectively the influence of tidal volume on the accuracy under otherwise constant conditions. As expected, the error increased with reduced tidal volume. It amounted to 1% at 1 L tidal volume and increased to 8% at 440 mL. This is equivalent to an error of the serial dead space determination of 20 mL or a remaining uncorrected synchronization error of about 20 to 25 ms. Reproducibility and asymmetry were unchanged.

DISCUSSION

One major obstacle to reliable measurement of FRC by gas washin and washout in an open system is the precise and synchronous measurement of gas flow and indicator gas concentration. Our study shows that the errors introduced by sample transport to a side stream sensor can be corrected with sufficient accuracy.

Frequently the absolute value of the FRC is of less interest than its trend or its change after e.g. a recruitment maneuver. Therefore, it could be argued that accuracy is less important than reproducibility or sensitivity. However, this conclusion is not correct. Any change of the ventilatory pattern or the mechanical properties of the lung will alter the errors introduced by poor synchronization. This change of the measurement errors would be misinterpreted as a true change of the FRC. Therefore, high accuracy is imperative for high sensitivity.

This study had its focus on the determination of the accuracy. The test conditions covered normal as well as extreme and partly clinically unrealistic worst-case conditions. This procedure was chosen because it can be expected that an instrument that shows sufficient accuracy under normal and extreme conditions will also be accurate under other realistic conditions.

Under the tested combinations of lung mechanics and ventilation parameters FRC can be determined with an accuracy that seems to be sufficient for clinical applications as well as for scientific studies. In most cases, the FRC could be determined with a bias of less than 5%. Variability was about 2 to 3%. The asymmetry, i.e. the difference between consecutive washins and washouts, was of the same magnitude. The presence of a large volume humidifier had no influence on the results although it slowed down the change of inspired concentration. As expected the measurement errors increased with decreasing volume or decreasing compliance, respectively. Nevertheless, they never reached a magnitude that could affect the clinical interpretation of the results.

The systematic errors were greatest at a very low compliance of 20 mL/mbar and high ventilatory pressures. Here the FRC was underestimated by approximately 5% during CMV at an unrealistically high tidal volume of 800 mL whereas it was overestimated by about the same amount during PCV at a moderate tidal volume of 400 mL. These errors can be expressed in terms of a remaining uncorrected synchronization error of about 20 to 25 ms or 10% of the delay fluctuations. Depending on the ventilatory pattern, these remaining errors may lead to an over- or underestimation of the FRC. At extremely low compliance, therefore, a drastic change of the ventilatory pattern can lead to an erroneous alteration of the measured FRC by up to 10%. However, such drastic changes of the ventilatory pattern are exceptional.

We conclude that also with a very low compliance, a change of the FRC can be detected with a resolution of typically 5%, provided the tidal volume is greater than 400 mL. At lower tidal volumes the errors increase and may reach up to 10% at tidal volumes of 300 mL. However, reproducibility is nearly unaffected by the test conditions. The variability amounts to approximately 2.5%.

The remaining errors are caused by the limitations of the response-time and delay correction. With the used sensor, the response-time depends slightly on the magnitude and direction of the concentration change. It is also affected by the flow through the sensor, which changes during each breath according to the cycling breathing pattern. This makes it difficult to predict under which conditions the FRC will be over- or underestimated.

This study focused on the technical aspects only and here mainly on the major technical issue, namely the distortion of the gas concentration measurement caused by positive pressure ventilation. It was shown that accurate measurement is possible even under simulated extreme ventilatory conditions.

The obtained accuracy has to be compared with that of other methods that can also be used with an open circuit. Tracer gases like SF_6 can be measured directly at the Y-piece with negligible response time and delay. Jonmarker *et al.* [3] and Larsson *et al.* [4] report a variability of about 1%. However, details of the experimental conditions are not given.

Zinserling *et al.* [5] have developed a system for nitrogen washout using a mass spectrometer as gas sensor. Data analysis was carried out off-line. At ventilatory pressures of 8 and 12 mbar they obtained essentially the same accuracy and reproducibility as we did under similar conditions.

Fretschner *et al.* [6], Eichler *et al.* [7] have published alternative methods for the compensation of the finite response time of slow O_2-sensors. The basic concept behind is that the waveforms of expired O_2 and CO_2 are nearly mirror images of each other. Therefore, the waveform of expired O_2 is estimated from the minimum and maximum O_2 fraction and the waveform of expired CO_2.

Fretschner *et al.* conclude that a 20% change of the FRC can be detected, provided tidal volume is kept constant. Both methods have the same drawbacks. Although the O_2- and CO_2-waveforms are nearly (inversely) congruent under steady state conditions this congruency may disappear during the first breathes of the washin/-out. In addition, this reconstruction can be performed only for the expiratory waveform. Assumptions must be made on the inspiratory waveform. However, the tubing system and humidifiers act as an additional compartment that smoothes and delays the concentration change at the Y-piece. This leads to gross systematic errors as described by Fretschner *et al.* It was therefore our aim to develop a system that does not impose constraints on the volume of the humidifier or the mode of ventilation, since such constraints would impede the clinical usability.

The major drawback of any procedure that requires an FiO_2 change results from the solubility of oxygen in the blood, which needs to be corrected. Lundin [12] has determined the rate at which nitrogen is eliminated from the blood and the tissue during oxygen breathing. He found that the body compartment with the shortest time-constant has a volume slightly greater than that of the blood, and that it is washed-out with a half-life of about 2 minutes. From these data and the solubility of oxygen, we estimate that under typical conditions the body stores for oxygen lead to a systematic overestimation of the FRC by 180 mL. Additional corrections, e.g. by SpO_2 measurement, may be required with patients having a low oxygen saturation.

Another drawback of any oxygen/nitrogen washin/washout is the requirement for stable circulatory conditions. Any change of cardiac output immediately before or during the measurement will change the oxygen content of the venous blood significantly. This change can be much greater than the usually small and correctable change of oxygen saturation induced by the changed F_iO_2 and the effect of the physical solubility of oxygen, and can lead to gross errors. Therefore, an FRC-measurement should not start immediately after a recruitment maneuver or a change of ventilator setting that can change cardiac output.

In this study, ventilation was constant in each series. Due to the nearly perfect gas mixing in the test lung, the tracing of the expiratory concentration showed a nice plateau. During assisted ventilation, however, tidal volume may fluctuate breath by breath. We expect, however, that the algorithm we have chosen is insensitive to this effect. The only assumption we have made is that the metabolic oxygen consumption is constant throughout the measurement. Therefore, neither fluctuating tidal volumes nor fluctuating end-tidal concentrations should have any effect on the results. It will be the task of clinical studies to investigate whether this expectation holds under clinical conditions.

In conclusion, we have shown that the FRC can be measured accurately by an automated procedure using only equipment approved for medical use. The sole manual action required was the change of inspired oxygen concentration. This procedure could be fully automated when integrated into an intensive care ventilator. Future clinical studies will reveal to which extent monitoring of the FRC can give valuable information for the treatment of patients in an intensive care unit.

APPENDIX A: LIMITATIONS COMMON TO NITROGEN AND OXYGEN WASHIN/WASHOUT

In a washin/washout based on a change of the inspired oxygen concentration the concentrations of the two complementary gases, nitrogen and oxygen, are changed simultaneously. Both gases can pass the alveolar wall. Since nitrogen is inert and nearly insoluble, a change in its alveolar concentration will hardly affect the blood content, thus no nitrogen is shifted from alveoli to blood or vice versa. In contrast, the blood oxygen content will change, the magnitude of change depending on the oxygen saturation at the lower FiO_2 level. Accordingly, the flow of oxygen from the lungs to the blood will change transiently during the measurement, despite constant oxygen consumption. This leads to concurrent transient changes of the difference between inspired and expired volumes.

With nitrogen as indicator gas, this volume difference is taken into account implicitly, because it is accompanied by an opposing change in the alveolar FN_2, i.e. the mass of nitrogen in the alveoli is conserved. When oxygen is used as the indicator gas, the volume difference requires explicit consideration. If this difference is known and taken into account, both procedures give the same result. However, the difference between inspired and expired volumes can change also for other reasons not related to a changed oxygen content of the blood. In modes like SIMV, the lung volume may change during the measurement. The intermittent large volume breaths can lead to a change of the lung volume that persists until the end of the measurement. Whereas a change of the oxygen saturation by 1% causes a change of the oxygen content of the blood by about 10 ml, the lung volume may change by several 10 or 100 ml during the measurement. These additional volume differences, which are not caused by the solubility of oxygen, would lead to great errors, if ascribed solely to a shift of oxygen between alveoli and blood.

Without information other than the volume signal, it is impossible to distinguish between the two factors. However, this distinction is essential since they require different mathematical consideration. If information on their

respective contribution to the volume change is lacking and the entire change is attributed to only one of them, errors are introduced to both the measurement via nitrogen and that via oxygen, i.e. the methodical differences between the insoluble gas nitrogen and the soluble gas oxygen vanish.

The following mathematical description of this connection disregards carbon dioxide, humidity and the constant oxygen consumption. Considering these factors would only complicate the mathematics without changing the results.

Every FRC-measurement with a blood-insoluble gas is based on the conservation of masses:

$$FRC \times C_{et,0} + \sum_{1}^{N} (V_{\text{insp},i} \times \bar{C}_{\text{insp}} - V_{\text{exp},i} \times \bar{C}_{\text{exp},i}) = FRC \times C_{et,N} \tag{1}$$

This leads to the well-known equation:

$$FRC = \frac{\sum_{1}^{N} (V_{\text{insp},i} \times \bar{C}_{\text{insp}} - V_{\text{exp},i} \times \bar{C}_{\text{exp},i})}{\Delta C_{et}} \tag{2}$$

The basis for these equations is the assumption that the end-expiratory volume of the lungs does not change during the measurement. If, however, the lung volume changes by ΔV_{lung}, Equations (1) and (2) need to be modified to:

$$FRC \times C_{et,0} + \sum_{1}^{N} (V_{\text{insp},i} \times \bar{C}_{\text{insp}} - V_{\text{exp},i} \times \bar{C}_{\text{exp},i}) = (FRC + \Delta V_{\text{lung}}) \times C_{et,N} \tag{1a}$$

$$FRC = \frac{\sum_{1}^{N} (V_{\text{insp},i} \times \bar{C}_{\text{insp}} - V_{\text{exp},i} \times \bar{C}_{\text{exp},i}) - \Delta V_{\text{lung}} \times C_{et,N}}{\Delta C_{et}} \tag{2a}$$

The term proportional to ΔV_{lung} vanishes only when the concentration of the used indicator gas is zero at the end of the measurement. This is the case in a complete nitrogen washout, when the inspired oxygen concentration is set to 100% and therefore the nitrogen concentration is zero. When, however, the measurement is carried out at a low FiO_2 (high nitrogen concentration) and the concentrations are altered by only by a small amount, a small value of ΔV_{lung}can lead to great errors of the calculated FRC. With e.g. an N_2-concentration of 80% and a small concentration step of 10%, the resulting FRC-error will amount to $8 \times \Delta V_{\text{lung}}$. It is therefore imperative to consider this volume change.

Unfortunately, the only information that is available for this correction is the accumulated difference between inspired and expired volumes, ΔV.

$$\Delta V = \sum_{1}^{N} (V_{\text{insp},i} - V_{\text{exp},i}) \tag{3}$$

This volume difference consists of two components. One is the change of lung volume during the measurement, ΔV_{lung}; the other the change of the oxygen content of the blood, ΔVO_2. However, measurable is only the sum of both:

$$\Delta V = \Delta V_{\text{lung}} + \Delta VO_2 \tag{4}$$

Although a nitrogen washin/washout is theoretically insensitive to any change of the oxygen content of the blood, ΔVO_2, this insensitivity is lost due to this ambiguity. The change of lung volume can only be assessed after ΔVO_2 is known. Because ΔVO_2 can be estimated only after the completion of the measurement, is seems preferable to perform the calculations in two steps. In the first step, ΔVO_2 is ignored and ΔV_{lung} is approximated by the measured total ΔV. In the second step, the result is corrected for the neglected parameter ΔVO_2 by:

$$\Delta FRC = \frac{\Delta VO_2 \times C_{et,N}}{\Delta C_{et}} \tag{5}$$

The same calculation can be performed for oxygen. The results are identical. This is not surprising, because the underlying assumptions are the same. In consequence, both complementary gases have the same limitations in common. With both gases, it is necessary to correct the results for the effect of a changed oxygen content of the blood, if this change is significant.

The necessary correction is proportional to the nitrogen concentration, irrespective of whether the inert gas nitrogen or the soluble gas oxygen is used. With patients who have low oxygen saturation ΔVO_2 may be significant. However, these patients are usually ventilated with a high FiO_2. Therefore, the nitrogen concentration is low. This compensates partly for the greater change of the oxygen content of the blood.

In the preceding, we have regarded a change of the lung volume as the predominant cause for a volume difference that is different from ΔVO_2. However, small accumulating measurement errors can also lead to such a volume difference. Although the mathematical corrections for the latter are different, they also require that ΔVO_2 is determined separately.

In conclusion, every method that is based on a change of the FiO_2 for determination of the FRC has the same

limitation in common. Irrespective of whether nitrogen or oxygen is used, the change of the oxygen content of the blood must be considered separately and be assessed by independent means.

APPENDIX B: DETERMINATION OF THE FRC

When FRC is determined by an oxygen washin or washout, the mass balance is described by the following equation:

$$FRC = \frac{\sum_{i=1}^{N} \left(M_{\mathrm{insp},i} - M_{\mathrm{exp},i} - T_i \times \Delta\right) + \Delta V_{\mathrm{lung}} \times (1 - C_{et,N}) - \Delta V}{C_{et,N} - C_{et,0}} \quad (1)$$

$C_{et,0}$ and $C_{et,N}$ are the end-tidal concentrations (fractions) of oxygen before and at the end of the maneuver, M_{insp} and M_{exp} are the inspired and expired amounts of oxygen and T is the duration of a breath. The term Δ represents the steady-state difference between inspired and expired fluxes of oxygen, i.e. oxygen consumption. However, since other factors like e.g. measurement errors also contribute to this difference, the parameter Δ serves mainly as a quantity that balances this steady-state difference, irrespective of the physiological or technical factors causing it. ΔV_{lung} is the change of the lung volume during the measurement; ΔV the accumulated difference between inspired and expired volumes (see Appendix A). Since the influence of an RQ different from 1.0 needs to be corrected independently (Mitchell *et al.*, 1982), the difference between ΔV and ΔV_{lung} is only given by the alterations of the oxygen content of the blood, ΔVO_2, caused to the changed FiO_2. Equation (1) can therefore be re-written to:

$$FRC = \frac{\sum_{i=1}^{N} (M_{\mathrm{insp},i} - M_{\mathrm{exp},i} - T_i \times \Delta) - \Delta V \times C_{et,N} - \Delta VO_2 \times (1 - C_{et,N})}{C_{et,N} - C_{et,0}} \quad (1a)$$

In the above formulas, we have neglected the small influence of the expired carbon dioxide concentration and the humidity of the gas on the end-tidal concentrations, because they contribute only to the factors proportional to ΔV and ΔVO_2, respectively. Consideration of these small corrections to the corrections had otherwise made the formulas unduly complicated.

Correct calibration of the oxygen sensor is not a critical issue. The amounts of oxygen and the end-tidal concentrations are measured by the same sensor. Therefore, an offset error is cancelled out by the subtraction and a sensitivity error by the quotient. When, e.g. all concentration readings are in error by the same factor, the gas amounts in the nominator and the concentrations in the denominator will change by the same factor, leaving the ratio unchanged. Thus, an uncalibrated sensor can be used, provided it has a linear response.

The inspired and expired amounts of oxygen are calculated by multiplication of flow by concentration. This requires that both signals are synchronous. Suitable flow sensors are standard components of modern ventilators. However, side-stream sensors exhibit a significant delay in the order of about 1 sec. Unfortunately, this delay is not constant. It changes during the measurement due to the changing gas viscosity (Brunner *et al.*, 1985). In addition, the cyclically alternating ventilatory pressure leads to a cyclic alteration of the delay. This can amount up to 10 to 20% of the mean delay or several 100 ms. Farmery and Hahn (Farmery and Hahn, 2001) have shown in a paper that was published after the completion of our study, that the gas concentrations are distorted in the time domain during positive-pressure ventilation. Both disturbing effects must be corrected sufficiently.

Patients who are expected to benefit most from a measurement of their FRC usually have restricted lungs with time constants $\tau = R \times C$ as short as 200 or 300 ms. It can be shown that under these conditions a synchronization error of e.g. 25 ms will cause a relative error of the FRC of about 10%. Therefore, the remaining error of synchronization should be less than 25 ms or 10% of the maximum fluctuation of the delay, respectively.

The method we have chosen for the calculation of the variable delay is different from that proposed by Farmery and Hahn and is based on a physical/mathematical model of the entire pneumatic circuit of the gas analyzer. A detailed description of all computational steps is beyond the scope of this paper. We therefore limit the description to what is essential for the understanding of the principle.

The gas concentration is sampled at a constant frequency with a fixed time interval *dt*. Therefore, the delay can be expressed in terms of the number *N* of samples. When the pressure at the Y-piece is zero, the gas flows at a constant speed U_0. With L = length of the tube and N_0 = delay at zero pressure we get:

$$L = N_0 \times U_0 \times dt \quad (2)$$

During positive pressure ventilation, the pressure gradient across the tube alternates. Therefore the speed U is not constant but is different for each sample "i". Since the distance L the gas sample has to travel is unchanged, Equation (2) has to be modified to:

$$L = \sum_{i=1}^{N} U_i \times dt \quad (3)$$

From that follows after elimination of L and dt :

$$\sum_{i=1}^{N} \frac{U_i}{U_0} = N_0 \tag{4}$$

The actual delay in terms of samples N is calculated by summation of the normalized speeds U_i/U_0 until this sum equals N_0. The issue is therefore the determination of the normalized speed for each sample. Since the speed U of the gas flow is proportional to the pressure gradient ΔP and inversely proportional to the mean gas viscosity η,the normalized speed is given by:

$$U_i/U_0 = (\Delta P_i/\eta i)/(\Delta P_0/\eta_0) \tag{5}$$

The parameters of this model are the pressure in the water trap at zero ventilation pressure, the volume of the water trap, the sample flow at zero ventilation pressure and the characteristics of the gas pump. With this model, the gas flow through the various components of the instrument is calculated continuously. From that follows the transit time of a gas sample from the Y-piece to the sensor. The finite response time of the oxygen sensor is corrected using its known step-response. The flow signals measured by the ventilator are further corrected for the influence of the gas composition on the flow reading. All other factors affecting accuracy are corrected with methods equivalent to those chosen by Mitchell.

The reconstructed O_2-concentration at the Y-Piece is shown in Figure 4. In this measurement, the serial dead space was zero. Therefore, the reconstructed concentration should change in a stepwise manner at the beginning of both inspiration and expiration. The average delay was about 800 ms. Note that the time-axis for the oxygen tracing is that after delay correction. Therefore, the calculated delay starts to decrease 800 ms before inspiration because the increased pressure accelerates all the gas samples that had entered the sampling tube before. The delay reaches a minimum value at the onset of inspiration. Thereafter it increases continuously showing a constant value about one second before the onset of expiration. The highest value is calculated at the transition from inspiration to expiration when the reduced pressure gradient slows down the movement of the gas in the tube. The difference between maximum and minimum delay is about 150 ms or 20% of the mean delay. The reconstructed concentration curve shows a 50% change exactly at the point where the ventilatory phases change. Although it does not show an ideal step change, the resulting synchronization error is small and negligible.

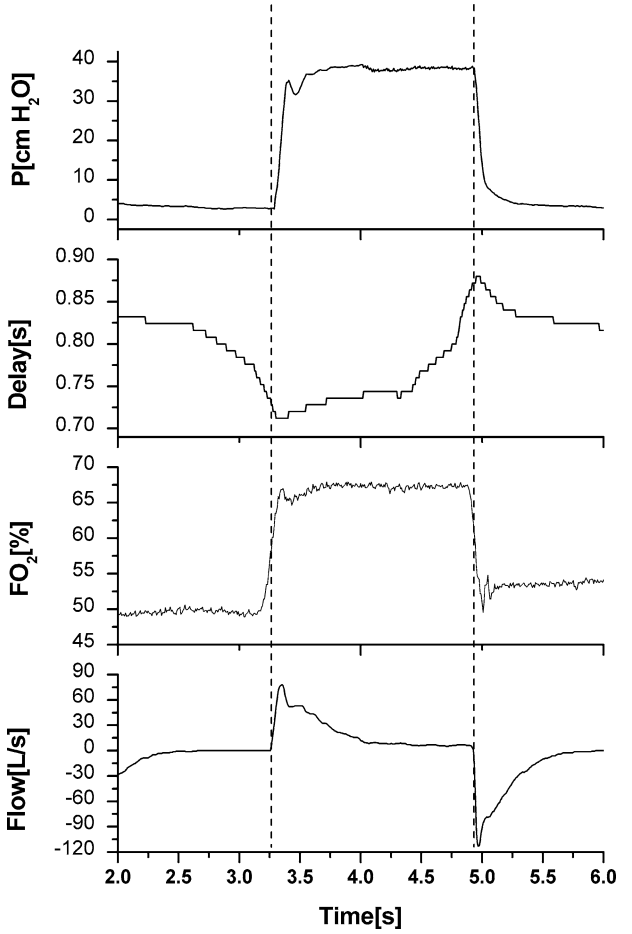

Fig. 4. Airway-pressure, calculated delay, reconstructed O_2-concentration and flow as function of time. The dashed lines mark start of inspiration or expiration, respectively.

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